Review of Patients with 50-69% Internal Carotid Artery Stenosis over a 3 Year Period

Nina Murray
Technological University Dublin

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Review of Patients with 50-69% Internal Carotid Artery Stenosis over a 3 Year Period

Nina Murray B.Sc

Dublin Institute of Technology
M.Phil. Clinical Measurement Science

Supervisors: Prof Pat Goodman
Dr Cleona Gray

School of Physics

September 2018
Declaration

I certify that this thesis which I now submit for examination for the award of Master of Philosophy, is entirely my own work and has not been taken from the work of others, save and to the extent that such work has been cited and acknowledged within the text of my work.

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Abstract

**Purpose:** Carotid artery stenosis (CAS) is defined as the presence of significant narrowing of the arteries of the extracranial carotid system due to the presence of atherosclerotic plaque and affects up to 10% of people over 65 years (Goessens et al 2007). Management of 50-69% stenosis is centred on medical optimisation and risk factor modification. Surgical intervention is typically reserved for patients with stenosis of > 70%.

The primary aim of the study is to determine if asymptomatic carotid artery disease causing a 50-69% internal carotid artery stenosis (ICAS) typically progressed to a >70% stenosis, thereby evaluating the necessity of annual Colour Duplex follow-up in patients presenting with a 50-69% stenosis. Additionally, the study aimed to determine if ultrasound monitoring of moderate ICAS provided markers able to identify any predisposing risk factors associated with progression of ICAS.

**Methods:** All Carotid Duplex scans performed in the Vascular Laboratory in the Mater Misericordiae University Hospital (MMUH) from January 2007 and December 2009 were retrospectively reviewed by the same experienced vascular physiologist. All patients who presented with unilateral or bilateral asymptomatic internal carotid artery stenosis of 50-69% on their first visit were included in this study and followed up until December 2011. Patients who presented with a non-haemodynamically significant internal carotid artery stenosis of <50% or >70% bilaterally, a history of carotid surgery or with no follow up scan performed were excluded from the study.

**Results:** The study examined the results of the scans of 4573 patients. Of the 4573 patients 876 were found to have a 50-69% stenosis at their initial scan. Of these, 287 patients were excluded from the study for various reasons leaving 589 patients in this study. Of the 589 patients included in the study, progression of ICAS was observed 17.3% of patients. A number of risk factors were analysed to determine their impact on disease progression. Positive smoking history, male gender and positive cardiac history were all found to have a significant correlation to disease progression.

**Conclusion:** As 17.3% of patients progressed to a >70% internal carotid artery stenosis over the course of the study it is evident that there was a significant rate of ICAS progression noted in this cohort of patients.
Acknowledgements

I would like to thank my supervisors, Dr Cleona Gray and Prof. Pat Goodman for their assistance and patience over the course of this project.

I would also like to thank the staff and consultants of the Vascular Laboratory in the Mater Hospitals, Public and Private, for all their help and support over the course of the Masters.

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List of Abbreviations

AF     Atrial Fibrillation
CABG   Coronary Artery Bypass Graft
CAS    Carotid Artery Stenosis
CCA    Common Carotid Artery
CVA    Cerebral Vascular Accident
CTA   Computed Tomography Angiography
CVD    Cardiovascular Disease
ECA    External Carotid Artery
ECST   European Carotid Surgery Trial
EDV    End Diastolic Velocity
HDL-C  High Density Lipoprotein Cholesterol
ICA    Internal Carotid Artery
IMT    Intima-Media Thickness
ICAS   Internal Carotid Artery Stenosis
LDL-C  Low Density Lipoprotein Cholesterol
MMUH   Mater Misericordiae University Hospital
MRA    Magnetic Resonance Angiogram
MRI    Magnetic Resonance Imaging
NASCET North American Symptomatic Carotid Endarterectomy Trial
NCHD   Non-Consultant Hospital Doctor
PSV    Peak Systolic Velocity
SHEP   Systolic Hypertension in the Elderly Program
TIA    Transient Ischemic Attack
TC     Total Cholesterol
TG     Triglycerides
Review of Patients with Asymptomatic 50-69% Internal Carotid Artery Stenosis over a 3 Year Period
Chapter I:

Introduction
CHAPTER I: INTRODUCTION

In Ireland, from 2006 to 2015 the incidence of mortality associated with cerebrovascular accident (CVA) has remained fairly static with CVA recorded as the cause of death in 1,947 cases in 2006 and 1,902 cases in 2015. Since 2010 CVA has been the third most common cause of death in Ireland, behind all cancers and ischaemic heart (Central Statistics Office, 2017). It is also the main cause of acquired physical disability in Ireland with an estimated 30,000 people living in the community with disabilities as a result of a stroke (Irish Heart Foundation, 2018), and with approximately 80% of CVA being ischaemic in nature (www.stroke.org.uk, 2015), internal carotid artery stenosis is an important area of study.

Ischaemic CVA is often the result of carotid artery stenosis (CAS), commonly defined as the presence of significant narrowing of the arteries of the extracranial carotid system due to the presence of atherosclerotic plaque (Goessens et al 2007). Management of internal carotid artery stenosis of 50-69% is centred on risk factor modification and medical optimisation while surgical intervention is typically reserved for patients with high-grade stenosis of > 70%.

There are a number of known risk factors for carotid artery disease including family history, older age, male gender, hypertension, smoking, hypercholesterolemia, heart disease, intima media thickening and diabetes (Wolff et al, 2007).

Internal carotid artery disease is often asymptomatic, with the first indication of disease being CVA or transient ischemic attack (TIA). TIA symptoms include loss of power, tingling, numbness, paralysis of the limbs and/or face, speech disturbances and/or visual disturbances (Goessens et al, 2007).
Colour duplex ultrasound is the established examination used for evaluation of internal carotid artery stenosis due to its non–invasive nature. Duplex ultrasound has been found to have a sensitivity of 98% and a specificity of 88% in identification of angiographic stenosis of ≥ 50% (Jahromi et al, 2005), while Henry et al (2015) reported a sensitivity of 95%, specificity of 90% in the diagnosis of 70-99% stenosis.

Currently all patients who attend the Vascular Laboratory in the Mater Misericordiae University Hospital (MMUH) for ultrasound investigation of their carotid arteries and present with asymptomatic internal carotid artery stenosis of 50-69% are entered into a long standing follow up programme. At this point interventions in the form of pharmacological therapy and lifestyle modifications such as smoking cessation are implemented. If the stenosis reaches >70% the patient is considered for surgical intervention in the form of a carotid endarterectomy.

1.1 Research Questions

1. Does asymptomatic carotid artery disease causing a 50-69% internal carotid artery stenosis typically progress to a >70% stenosis?

2. Is it possible to identify the proportion of patients who go on to develop symptomatic or asymptomatic >70% internal carotid artery stenosis or require surgical intervention?

3. Is there a benefit to annual Colour Duplex follow-up in patients presenting with an asymptomatic 50-69% internal carotid artery stenosis?

4. Is the current follow up programme in the MMUH effective in the detection of internal carotid artery stenosis progression?

5. Is it possible to identify any predisposing risk factors associated with progression of ICAS?
Chapter II:

Literature Review
CHAPTER II: LITERATURE REVIEW

In order to fully understand the importance of internal carotid artery stenosis (ICAS) in relation to cerebrovascular disease, it is beneficial to be familiar with the anatomy of the extracranial carotid anatomy, the risks associated with internal carotid artery stenosis and the methods of treatment of ICAS. These topics will be covered in section 2.1 of this chapter.

Following this, in section 2.2 the current literature will be reviewed with regards to progression of ICAS, risk factors associated with ICAS and the current guidelines for best practice in both following up and treating ICAS.

2.1 Anatomy of the Extracranial Circulation

The extracranial circulation arises from the aortic arch. In the following diagram, figure 2.1 on the right hand side, the Brachiocephalic artery arises from the arch and just above the right clavicle bone it bifurcates into the right subclavian artery and the right common carotid artery. On the left hand side, the common carotid and subclavian arteries arise directly from the aortic arch (fig. 2.1).

Figure 2.1: Extracranial Carotid Circulation

(http://www.vascularultrasound.net/vascular-anatomy/arteries/extracranial
The vertebral arteries supply a large part of the posterior circulation of the brain and arise from the subclavian arteries (fig. 2.1). They course superiorly through the transverse processes of the spine and join to form the basilar artery.

The common carotid arteries are the principle arteries in the neck. They ascend obliquely on either side of the trachea, from just above the clavicle to the top of the thyroid cartilage, where each divides into two branches, the internal and the external carotid arteries.

The external carotid artery (ECA) supplies the exterior of the head, face and neck.

The internal carotid artery (ICA) supplies the main circulation to the brain and eyes, and is the artery that will be discussed throughout this study.

### 2.1.2 Carotid Artery Stenosis

Carotid artery stenosis is the result of a build-up of atherosclerotic plaque causing a narrowing of the vessel. Atherosclerosis is a degenerative disease of the arteries in which plaque develops on the inner wall of the vessel narrowing the lumen and impeding blood flow. This may progress to total obstruction of the lumen. Plaque formation is most likely to occur where a blood vessel bifurcates.

### 2.1.3 Symptoms of Internal Carotid Artery Stenosis

Internal carotid artery stenosis (ICAS) is often asymptomatic, with the first indication of disease being stroke or transient ischemic attack (Goessens et al, 2007). Symptoms are outlined below in sections 2.1.3.1 and 2.1.3.2. Symptoms resolving in <24hours are categorised as a Transient Ischaemic Attack (TIA). Symptoms resolving in >24hours or where the deficit is permanent are categorised as a Cerebrovascular Accident (CVA) or
Review of Patients with Asymptomatic 50-69% Internal Carotid Artery Stenosis over a 3 Year Period

Stroke. Symptoms lasting >24 hours but where there is full recovery is categorised as a recovered cerebrovascular accident.

2.1.3.1 Non Focal Symptoms

Non-focal symptoms are difficult to assign to one hemisphere of the brain. They are often associated with damage to the brainstem or posterior circulation of the brain. Symptoms may be transient or permanent and are outlined below in table 2.1.

Table 2.1: Non-Focal Symptoms

<table>
<thead>
<tr>
<th>Visual</th>
<th>Bilateral transient vision loss or impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bilateral retinal ischaemia</td>
</tr>
<tr>
<td>General</td>
<td>Bilateral motor or sensory changes</td>
</tr>
<tr>
<td></td>
<td>Dysarthria</td>
</tr>
<tr>
<td></td>
<td>Syncope</td>
</tr>
<tr>
<td></td>
<td>Blackouts</td>
</tr>
<tr>
<td></td>
<td>Vertigo, Dizziness, light-headedness</td>
</tr>
<tr>
<td></td>
<td>Ataxia (unsteady gait)</td>
</tr>
<tr>
<td></td>
<td>Memory problems</td>
</tr>
<tr>
<td></td>
<td>Confusion or behavioural changes</td>
</tr>
</tbody>
</table>

2.1.3.2 Focal Symptoms

Focal symptoms relate to one side of the body and are typically attributed to problems in one hemisphere of the brain. Symptoms can be transient or permanent in duration and are categorised accordingly.

Symptoms are outlined on the next page in table 2.2
Table 2.2: Focal Symptoms

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>EXPLANATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemiplegia</td>
<td>Paralysis of one side of the body</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>Severe weakness of one side of the body</td>
</tr>
<tr>
<td>Monoparesis</td>
<td>Severe weakness of one limb</td>
</tr>
<tr>
<td>Hemi sensory Deficit</td>
<td>Loss of sensation on one side of the body</td>
</tr>
<tr>
<td><strong>Visual Disturbance</strong></td>
<td></td>
</tr>
<tr>
<td>Transient Monocular Blindness</td>
<td>Transient shadow or curtain blocking all or part of the visual field in one eye</td>
</tr>
<tr>
<td>Central/Retinal Branch Occlusion</td>
<td>Permanent loss of all or part of the visual field in one eye</td>
</tr>
<tr>
<td>Retinal Emboli</td>
<td>Loss of a visual field of which patient may or may not be aware</td>
</tr>
<tr>
<td>Homonymous Hemianopia</td>
<td>Transient or permanent loss of one lateral field of vision affecting both eyes simultaneously</td>
</tr>
<tr>
<td><strong>Speech Problems</strong></td>
<td></td>
</tr>
<tr>
<td>Expressive Dysphasia</td>
<td>Difficulty expressing speech or written word</td>
</tr>
<tr>
<td>Receptive Dysphasia</td>
<td>Difficulty understanding verbal or written word</td>
</tr>
<tr>
<td>Aphasia</td>
<td>Unable to speak or write or understand simple commands</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>Slurred Speech</td>
</tr>
<tr>
<td>Horner’s Syndrome</td>
<td>Drooping upper eyelid, elevated lower eyelid, dilation of iris, lack of perspiration on one side of face only.</td>
</tr>
</tbody>
</table>

2.1.4 Treatment

There are currently 2 types of treatment available for elective repair of internal carotid artery stenosis, surgical and radiological. The surgical option is carotid endarterectomy. There are two radiological options; carotid angioplasty and carotid stenting. Elective
repair is currently recommended for symptomatic >50% stenosis and asymptomatic >70% stenosis.

2.2 Review of Current Literature

As is now evident, the internal carotid arteries are the main vessels supplying blood to the brain, and internal carotid artery stenosis can result in cerebrovascular accident. Cerebrovascular accident (CVA) was the third most common cause of death in Ireland from 2010 to 2016 and resulted in almost 3 times as many deaths as breast cancer in that time (Central Statistics Office, 2017). CVA is the also the main cause of acquired physical disability in Ireland with an estimated 30,000 people living in the community with disabilities as a result of a stroke (Irish Heart Foundation, 2018), and with approximately 80% of CVA being ischaemic in nature (www.stroke.org.uk, 2015), internal carotid artery stenosis is an important area of study.

In this section, the current literature will be reviewed with regards to prevalence of ICAS, the progression of ICAS, the risk factors associated with ICAS and the current guidelines for best practice in both following up and treating ICAS.

2.2.1 Carotid Artery Stenosis

Carotid artery stenosis (CAS) is commonly defined as the presence of significant narrowing of the arteries of the extracranial carotid system due to the presence of atherosclerotic plaque (Goessens et al, 2007). Atherosclerosis is an inflammatory disease that may persist for several years before clinical manifestations, such as CVA, myocardial infarction or peripheral arterial disease, become evident (Puddu et al, 2005).
Atherosclerosis is a vascular disease that results in plaque formation caused by deposits of lipids in the sub endothelial space, presumably from increased permeability of the lining endothelial cells. Excess serum low density lipoprotein cholesterol (LDL-C) in the artery is retained in the intima, most often at sites of hemodynamic strain. Hemodynamic strain and the accumulation of lipids may result in the initiation of an inflammatory process in the artery (Ross, 1999). If hypercholesterolemia is not controlled, particularly in the presence of additional risk factors such as those outlined in section 2.2.5, then the inflammatory response will continue, and if the conditions that induced the response continue long enough, remodelling of the lesion may occur and a fibrous plaque may intrude into the artery wall (Ross, 1999).

Fatty streaks, the precursors to plaques, are prevalent in young people despite remaining clinically silent, and may progress to form atherosclerotic plaque or may eventually disappear. Atherosclerosis is a process that begins in childhood and obesity is an independent factor that increases risk of atherosclerosis. Endothelial dysfunction precedes the manifestations of atherosclerosis by many years.

2.2.1.1 Risks Associated with Internal Carotid Artery Stenosis

Internal carotid artery disease is often asymptomatic, with the first indication of disease being CVA or transient ischemic attack (TIA). Symptoms, as outlined above in sections 2.1.3.1 and 2.1.3.2, include loss of power, tingling, numbness, paralysis of the limbs and/or face, speech disturbances and/or visual disturbances (Goessens et al, 2007).

TIA is defined by the American Heart Association and the American Stroke Association (Easton et al, 2009) as a brief episode of neurological dysfunction resulting from cerebral ischaemia not associated with permanent cerebral infarct. Previously TIAs
were defined as any cerebral event with symptoms lasting less than 24 hours, and this is still the commonly used definition until acute infarction can be confirmed or ruled out by magnetic resonance imaging (MRI).

CVA is defined as an episode of neurological dysfunction resulting from cerebral ischaemia associated with permanent cerebral infarct (Easton et al, 2009). Previously symptoms lasting longer than 24 hours were considered to be indicative of CVA but, as with TIA, the presence of permanent cerebral infarct is the defining criteria.

### 2.2.2 Prevalence, Morbidity and Mortality

Internal carotid artery stenosis (ICAS) prevalence increases from the age of 50 years onwards and affects approximately 7% of women and more than 12% of men over 70 years of age. Patients with ICAS are at increased risk of ipsilateral carotid territory ischaemic stroke (Marquardt et al, 2010).

Each year, approximately 10,000 Irish people have a CVA or TIA and approximately 2,000 of these people die as a result of this (Irish Heart Foundation, 2018). TIA and CVA are responsible for over 7,000 hospitalisations in Ireland every year and approximately 20% of these patients (~1,400 patients) die as an inpatient in hospital (McElwaine et al, 2015). Approximately 80% of CVA are ischaemic in nature and occur as a result of significant stenosis of the vessels of the intracranial or extracranial circulation (www.stroke.org.uk, 2015).

The incidence of mortality associated with CVA has remained fairly static since 2007 with CVA recorded as the cause of death in 2,087 cases in 2007 and 1,920 cases in 2016. Since 2007 CVA has been the third most common cause of death in Ireland, behind all cancers and ischaemic heart disease and since 2010, is in fact responsible for two and a half time more deaths annually than breast cancer (Central Statistics Office,
2017). CVA is also the biggest cause of acquired physical disability in Ireland with an estimated 30,000 people living in the community with disabilities as a result of a CVA (Irish Heart Foundation, 2018).

2.2.3 Ultrasound Screening and Surveillance

Duplex ultrasound is the established examination used for evaluation of internal carotid artery stenosis due to its non–invasive nature and has been found to have a sensitivity of 98% and a specificity of 88% in identification of angiographic ICA stenosis of ≥ 50% (Jahromi et al, 2005), and a 94% sensitivity and 90% specificity for detecting a >70% ICA stenosis (Jaff, 2008).

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) reported a clear benefit to performing carotid endarterectomy on symptomatic patients with a 70% to 99% angiographic ICA stenosis in comparison to medical treatment (Moneta et al, 1993). Further research by Moneta et al (1993) compared carotid angiograms with carotid duplex ultrasound scans of 100 patients using the NASCET criteria. The NASCET trial calculated the angiographic stenosis by measuring the residual lumen diameter at the site of the greatest narrowing and expressing it as a percentage of the patent lumen diameter measured distal to the bulb. By comparing this measurement to the velocity measurements obtained through colour duplex ultrasound (PSV, End Diastolic Velocity (EDV) and ICA/Common Carotid Artery (CCA) ratio) they were able to establish a diagnostic criteria for duplex ultrasound that had a high degree of sensitivity in detecting ICA stenosis of >70%. An ICA /CCA ratio of >4.0 on duplex ultrasound was found to have a sensitivity of 91% and a specificity of 87% in identification of 70% to 99% ICA stenosis (Moneta et al, 1993). Advances in ultrasound
technology may be responsible for the increased sensitivity reported by Jahromi et al (2005).

Muto et al (1996) examined the correlation between Magnetic Resonance Angiogram (MRA) and duplex ultrasound in diagnosis of surgically significant ICA stenosis (>60%) and found a high degree of correlation ($r = 0.87$). They found no significant difference in the accuracy of the two modalities in cases of >70% stenosis and suggest that duplex ultrasound is sufficient for preoperative evaluation of internal carotid artery stenosis. Clevert et al (2006) demonstrated that both MRA and colour duplex ultrasound tend to overestimate ICA stenosis of >90%, while MRA can mistake a high grade stenosis causing a <1mm residual lumen diameter for complete occlusion, and concluded a combination of colour duplex ultrasound and MRA are generally sufficient in unclear cases.

Computed Tomography Angiography (CTA) is also used in the diagnosis of ICAS, and has been found to have a sensitivity of 85% and a specificity of 93% in the detection of a 70% to 99% ICA stenosis (Jaff, 2008). CTA has also demonstrated a high degree of accuracy (85%) in differentiating between ‘trickle flow’ and total occlusion, which may be because its high spatial resolution is unaffected by low volume flow (Jaff, 2008). Titiel et al (2007) assessed the degree of agreement between colour duplex ultrasound and CTA and found a 79.1% agreement overall but found that this varied for different degrees of stenosis. They concluded that while colour duplex ultrasound is the first-line non-invasive imaging modality, CTA is beneficial when limitations such as calcification are taken into account. A study by Belsky et al, (2000) showed that colour duplex ultrasound has a sensitivity of 78.9% and a specificity of 96.3% when compared to CTA. They found that disagreement between modalities which would affect surgical intervention occurred in 10 out of 92 of cases (11%), with CTA proving to be more
accurate in detecting extremely low volume flow distal to a high grade stenosis. Belshy et al (2000) concluded that while CTA largely has no role in patients with mild or moderate stenosis, it may be an important addition to colour duplex ultrasound in patients with severe stenosis or occlusion when endarterectomy is being considered.

Duplex ultrasound is the established examination used for evaluation of internal carotid artery stenosis due to its non–invasive nature, although MRA and CTA are also used.

2.2.4 Asymptomatic 50-69% Internal Carotid Artery Stenosis

There is much debate concerning the most appropriate treatment for asymptomatic internal carotid artery stenosis. Patients with asymptomatic ICAS are generally considered low risk for ipsilateral neurological events, but this is not always the case.

2.2.4.1 Rate of Progression

Several studies have been conducted into determining the rate of progression of ICA stenosis, with results varying from insignificant progression to 25.2% progression over the duration of the studies. The risk factors that correlate with progression also vary amongst studies.

Laipis et al (2000) examined 442 carotid arteries over a 7 year period and found that progression of ICA stenosis occurred in 19% of patients in their study over that time frame. ICAS progression was found to correlate to coronary artery disease and with the ultrasound characteristics of the plaque imaged.

A study by Hicks et al (2015) conducted over 7.5 years found that 25.2% of their 258 patients progressed from moderate to severe disease and implicated tobacco use and dual anti platelet therapy as independent risk factors in ICAS progression.
Jahromi et al (2009) studied 547 patients over 4 years and concluded that the average rate of progression over a 2 year period was not significant, but was greater in diabetics with an initial ICA stenosis of >50% who continued to smoke.

Mulak et al (1999) found that risk of progression of ICA stenosis increased with time (9.3% per annum) and that the main variables effecting progression of ICA stenosis were ipsilateral ICA stenosis of >50%, contralateral ICA stenosis of >50%, ipsilateral external carotid artery (ECA) stenosis of >50% and systolic blood pressure of >160mmHg.

An ultrasonic measurement that has been shown to predict the progression of ICA stenosis is end diastolic velocity (EDV). Despite their small sample size of 56 patients, Moneta et al (1989) showed an EDV of >180cm/sec to correlate strongly with subsequent ICA occlusion when compared to EDV of <180cm/sec.

A study by Mansour et al (1999) showed disease progression to >80% in 15.5% of their 344 patients, with high initial peak systolic velocity (PSV) and EDV noted in the ICA that showed disease progression.

Nehler et al (1996) studied 263 patients over a period of 4 years and found that asymptomatic ICAS with an initial PSV of <175cm/sec had a 94% rate of freedom from progression compared with a 14% rate of freedom from progression in those with an initial PSV of ≥175cm/sec.

Winter et al (2016) followed 621 carotid arteries with a moderate stenosis of 50-79% over 5 years, and suggested that a PSV ≥165 cm/s is an ideal threshold value for defining high risk of progression over a period of 2 years.

Conrad et al (2013) discovered that despite optimal medical therapy 45% of the 794 patients in their study experienced progression of ICAS or developed ipsilateral symptoms.
2.2.4.2 Associated Risks

A study by Balestrini et al (2013) aimed to evaluate whether ultrasound monitoring of moderate asymptomatic ICAS would help identify patients at high risk for CVA, and determined that the one-year progression rate is related to a higher risk of vascular events, namely CVA. These findings were confirmed by Muluk et al (1999) and Kakkos et al (2014) who determined that progression of ICAS identified a group with twice the risk of ipsilateral CVA compared to those with no progression. Laipis et al (2000) also found that neurological events occurred with greater frequency in patients with disease progression when compared to patients with stable lesions.

2.2.5 Risk Factors

Risk factors for the development of carotid artery disease include family history, older age, male gender, hypertension, smoking, hypercholesterolemia, obesity, heart disease, and diabetes (Wolff et al, 2007). These risk factors have been well established in the development of atherosclerotic plaque, particularly in coronary artery disease; however the same principles apply for the development of carotid artery disease.

2.2.5.1 Gender and Age

Cerebrovascular events are more prevalent in men than in women. In general men also have a higher rate of age specific CVA incidence rates than women, except between the ages of 35-44 years and in those over 85 years of age (Goldstein et al, 2001). Oral contraceptive use and pregnancy account for the increased stroke risk in women aged 35-44 years.
The cumulative effects of aging and the progressive nature of stroke risk factors over time increase CVA risk, with CVA risk doubling in each successive decade after 55 years of age.

**2.2.5.2 Smoking**
Current smoking has long been recognised as a risk factor for development of atherosclerosis due to its ability to affect the systemic vasculature and the composition of blood. Smoking is the greatest avoidable risk factor for the development of atherosclerosis, as it causes reduced blood vessel compliance leading to increased arterial wall stiffness, increased platelet aggregation, decreased high density lipoprotein cholesterol levels, and increased fibrinogen levels (Goldstein et al, 2001). Numerous studies have demonstrated a substantial increase in risk of CVA associated with smoking with smokers having an approximately 1.8 fold increase in CVA risk in comparison to non-smokers. However this risk appears to be reversible with the Framingham Heart Study showing that at 5 years from cessation CVA risk has returned to the level of non-smokers (Goldstein, 2001)

**2.2.5.3 Hypertension**
Hypertension is related to an increase in the haemodynamic stress placed on artery walls. This in turn results in direct physical damage of the endothelial cells which can expose the sub endothelial cells to platelets and blood coagulation factors, the starting point in the development of atherosclerotic plaque (Crowther, 2005). Hypertension is a risk factor for CVA, with the incidence of CVA increasing in proportion to both systolic and diastolic blood pressures. Elevated systolic blood pressure has been shown to increase stroke risk with and without elevation in diastolic
blood pressure, making isolated systolic hypertension (systolic blood pressure >160mmHg, diastolic blood pressure <90mmHg) a key risk factor for CVA (Goldstein et al, 2001). Systolic blood pressure tends to increase with advancing age and the Systolic Hypertension in the Elderly Program (SHEP) demonstrated a 36% reduction in the incidence of CVA in patients being treated with antihypertensive medication (SHEP Cooperative Research Group, 1991).

2.2.5.4 Cholesterol

Cholesterol serves several important functions in the body. It is required by every cell in the body as it is an important part of cell membranes (Seeley et al, 2003). It also forms the basis of steroid hormones such as oestrogen, progesterone and testosterone (Durstine et al, 2002). Approximately 85% of the cholesterol needed by the body is produced endogenously, leaving only 15% to be obtained from ingested food. However when people consume more cholesterol from their diets than is necessary, the excess cholesterol enters the bloodstream and results in increased levels of serum lipids, particularly low density lipoprotein cholesterol (LDL-C) and triglycerides (TG), which is indicative of increased risk of developing atherosclerotic plaques and type 2 diabetes (Fernandez et al, 2005; Ashen and Blumenthal, 2005).

The National Cholesterol Education Program (ATP III) has produced guidelines for the optimal levels of serum lipids (Total Cholesterol (TC) <200mg\(\text{dl}\), LDL-C <100mg\(\text{dl}\), HDL=C ≥60mg\(\text{dl}\), TG <150mg\(\text{dl}\)), and the levels that can be considered to increase the risk of developing vascular disease or type 2 diabetes (TC >200mg\(\text{dl}\), LDL >100mg\(\text{dl}\), HDL ≤60mg\(\text{dl}\), TG >150mg\(\text{dl}\)) (Stone et al, 2005).
2.2.5.5 Obesity

Obesity results from an imbalance in energy intake and energy expenditure, and is affected by both environmental and genetic factors. Obesity represents one of the most serious global health issues with approximately 310 million people presently affected. Throughout Europe over 300,000 deaths annually are attributable to obesity, which is approximately 1 in every 13 deaths recorded (Speakman, 2004).

Obesity levels in Ireland are increasing. Approximately 33% of those over 18 years of age in Ireland were classified as overweight (15% classified as obese) in 2002, and this had increased to 36% (14% classified as obese) by 2007 (Morgan et al, 2008). These increases are often attributed to changes towards a more sedentary lifestyle as well as dietary changes that have occurred over the last 100 years.

Abdominal obesity can result in decreased HDL-C levels and also to an increase in small dense LDL-C particles (Ashen and Blumenthal, 2005). Small dense LDL-C particles have displayed increased arterial wall retention and increased susceptibility to oxidation (Kolovou et al, 2005) leading to an increased susceptibility to atherosclerotic plaque progression.

As well as having a significant impact on serum cholesterol levels, obesity is a risk factor for conditions such as hypertension and type 2 diabetes that increase the risk of atherosclerotic plaque formation (Speakman, 2004). As such, the association between obesity and vascular diseases is well established.

2.2.5.6 Diabetes

Insulin dependent diabetics have an increased susceptibility to atherosclerosis development and to risk factors which influence atherosclerotic plaque progression, namely hypertension, obesity, and hypercholesterolemia.
Elevated TG and reduced HDL-C are characteristic of diabetes (Laakso, 2002), with a prevalence 2-3 times higher in individuals with diabetes than those without. Diabetics will often have a different LDL-C particle size distribution to non-diabetic persons, which is apparent as an increased level of small dense LDL-C particles, which are highly atherogenic (Carmena, 2005).

Hypertension in particular is thought to increase the frequency of diabetic complications including CVA, with the American Stroke Association recommending careful control of hypertension in diabetics (Goldstein, 2001).

2.2.5.7 Cardiac Disease

Atrial fibrillation (AF) is a common cardiac arrhythmia and is a common cause of CVA. It is estimated that approximately two thirds of CVAs that occur in patients with AF are cardioembolic in nature and that AF is responsible for approximately 50% of embolic strokes. Other cardiac diseases that pose a risk of embolic CVA are dilated cardiomyopathy, valvular heart disease, and intracardiac congenital defects such as patent foramen ovale, while between 1% and 7% of patients undergoing cardiac surgery suffer from perioperative CVA (Goldstein et al, 2001).

Goldstein (2001) also reports that based on the Framingham Heart Study, 8% of men and 11% of women will have a CVA within 6 years of having an acute myocardial infarct, although this can often be attributed to the development of AF.

2.2.5.8 Family History

Family history of CVA may be associated with increased CVA risk. This may be due to genetic factors such as the inheritance of susceptibility of risk factors, as well as lifestyle factors and the interaction between environmental and genetic factors.
Due to the retrospective nature of the study family history was frequently not adequately recorded and was therefore not assessed during this study.

**2.2.5.9 Intima Media Thickness**

Intima Media thickness (IMT) is defined as the distance between the lumen-intima interface and the media-adventitia interface (Robertson et al, 2012), the hypothesis being that as atherosclerosis is a process that affects the arterial wall, IMT represents subclinical vascular disease. Several studies have found that stroke risk increases with increasing IMT (Bots et al, 1997; Gardin et al, 2014; Robertson et al, 2012), however due to the retrospective nature of this study this parameter was not assessed.

**2.2.5.10 Impact of Risk Factors**

A number of studies have examined the effect of several risk factors on ICAS progression but the results are inconsistent.

Laipis et al (2000) examined the impact of various risk factors on the rate of internal carotid artery stenosis progression and determined that there was no statistically significant correlation between age, gender, diabetes, hypertension, hypercholesterolemia and smoking, and rate of progression. They did however find that ultrasonic plaque characteristics correlated with rate of ICAS progression. Garvey et al (2000) found that an increase in pulse pressure and a decrease in HDL-C were the only independent predictors of carotid plaque progression. Hicks et al (2015) found tobacco use and antiplatelet use to be predictors of ICAS progression and Jahromi et al (2009) found that diabetics who smoked were more like to experience disease progression. As a result there is no definitive consensus on the impact of the various risk factors on ICAS progression.
2.2.6 Surveillance Guidelines

2.2.6.1 Society of Vascular Surgery Guidelines

The Society for Vascular Surgery guidelines (Ricotta et al, 2011) currently recommends medical management and surveillance for asymptomatic patients with a 50% to 60% stenosis, and for asymptomatic patients at high risk for intervention or with less than three years life expectancy.

Carotid endarterectomy is recommended for most asymptomatic patients with a 60% to 99% stenosis and symptomatic patients with a 50 to 99% stenosis (Ricotta et al, 2011). Internal carotid artery stenting should be reserved for symptomatic patients with 50% to 99% stenosis at high risk for carotid endarterectomy for anatomic or medical reasons, and is not currently recommended for patients with asymptomatic stenosis (Ricotta et al, 2011).

2.2.6.2 Follow Up Guidelines

There are no specific follow up interval guidelines currently outlined by the Society for Vascular Surgery however research by Strandness (2001) showed that patients with a <50% stenosis should be followed up annually while patients with a 50-79% stenosis should be followed up 6-monthly. Jahromi et al (2009) suggest that the average rate of stenosis progression over 2 years is not significant and therefore follow up colour duplex scans should be performed at 1-2 year intervals.

Nehler et al (1996) showed that an internal carotid artery PSV of ≥175cm/sec indicated a higher risk of early progression and recommends early vascular laboratory follow, however does not suggest a follow up interval. Similarly a study by Lovelace et al (2001) showed that patients with < 60% ICA stenosis and a PSV of ≥175cm/sec are more likely to progress to a higher grade stenosis and thus warrant 6-monthly follow up
scans, while patients with < 60% ICA stenosis and a PSV of <175cm/sec may benefit from follow up scans every 2 years.

### 2.2.6.3 Mater Misericordiae University Hospital Guidelines

Currently all patients who attend the Vascular Laboratory in the Mater Misericordiae University Hospital for ultrasound investigation of their carotid arteries and present with significant internal carotid artery stenosis of 50-69% are entered into a long standing follow up programme, as outlined in Table 2.3.

<table>
<thead>
<tr>
<th>Carotid Stenosis</th>
<th>Follow up period</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50%</td>
<td>No follow up</td>
</tr>
<tr>
<td>50-69%</td>
<td>Yearly</td>
</tr>
<tr>
<td>70-80%</td>
<td>6 monthly</td>
</tr>
<tr>
<td>&gt;80%</td>
<td>3 monthly</td>
</tr>
</tbody>
</table>

If or when the ICA stenosis reaches >70% the patient is considered for surgical intervention. Intervention is most commonly in the form of a carotid endarterectomy.

### 2.2.7 Risk Factor Modification and Medical Therapy

Management for ICA stenosis of 50-69% is centred on medical optimisation and risk factor modification, with surgical intervention typically reserved for symptomatic patients with high-grade stenosis of > 70% due to the durable benefit shown after eight years of follow-up (Barnett et al, 1998).
2.2.7.1 Risk Factor Modification

Risk factor modification includes lifestyle modifications in the form of smoking cessation, nutritional advice, weight management, and exercise. The risks associated with smoking and obesity are outlined above in sections 2.2.5.2 and 2.2.5.5 respectively, and detail the importance of smoking cessation and weight management with respect to prevention of atherosclerotic plaque formation. Weight management and nutrition go hand in hand, with diet playing an important role in weight management as well as affecting cholesterol levels (Stone et al, 2005). Proper nutritional advice is essential to risk factor modification.

Exercise can also have a positive influence of cholesterol levels, which are discussed above in section 2.2.5.4, by causing an increase in high density lipoprotein cholesterol (HDL-C) levels and a decrease in LDL-C, as well as decreasing blood pressure, and reducing the risk of type 2 diabetes and obesity (Thompson et al, 2003).

2.2.7.2 Medical Therapy

Medical optimisation focuses on ensuring patients are taking the correct medications or combinations of medications in the correct dosages to treat their conditions and, in the case of ICAS, includes prescribing medications to control hypertension, hypercholesterolemia and diabetes, as well as nonsteroidal anti-inflammatory drugs which serve to reduce blood viscosity and reduce the inflammatory markers involved in atherosclerotic plaque formation and progression (Altman and Scazziot, 2003).

Conrad et al (2013) examined the progression if ICA stenosis in asymptomatic patients with ICAS of 50%-69% over a 6 year period in order to examine if optimal medical therapy could reduce stroke risk. Optimal medical therapy was taken as achieved if the patient was on aspirin and a statin and consistently had a LDL-C level of <100mg/dL.
At the 5 years follow up point they concluded there was no benefit to optimal medical therapy when compared to the control group, as ICAS progression or ipsilateral symptoms occurred in 45% of patients. The study did however show that statins had a protective effect ($p = 0.0004$).

Hicks et al (2015) examined various risk factors thought to affect ICAS progression, including statin use, aspirin use and dual antiplatelet therapy use. Contrary to Conrad et al (2013), Hicks et al (2015) found no significant relationship between statin use and ICAS progression. Aspirin use was also not a significant predictor of disease progression; however they found that risk of progression was higher in patients receiving dual antiplatelet therapy.

Park et al (2016) identified 124 patients with asymptomatic moderate carotid stenosis and assessed their progression over a 5 year period. They reported progression in 31.8% of the arteries during the study timeframe, and no significant difference noted with statin and aspirin use.

Singh et al (2015) followed 214 patients with moderate or severe CAS to determine rate of progression with optimal medical therapy. The median length of follow up was 13 years and progression of stenosis was reported in 67.9% of vessels over this time frame.

Marquardt et al (2010) studied the risk of ipsilateral stroke in patients with $\geq 50\%$ asymptomatic ICAS on intensive medical therapy (antiplatelet and statin, antihypertensive and diabetic medication if required), and found that the average annual risk of stroke was 0.34% for an ipsilateral stroke and 1.78% for an ipsilateral TIA. They questioned if a benefit from surgery would remain if stroke risk is this low on optimal medical therapy.
2.2.8 Surgical Intervention

Current guidelines for the treatment of internal carotid artery stenosis is based on the results of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST), both of which demonstrated a highly beneficial effect of carotid endarterectomy in patients with high-grade carotid stenosis (Rothwell et al, 2003).

Carotid endarterectomy has long been considered the gold standard treatment for internal carotid artery stenosis with a proven record in reducing both mortality and morbidity; however internal carotid artery stenting has emerged as a less invasive alternative that may be more attractive for patients with high perioperative risk.

2.2.8.1 North American Symptomatic Carotid Endarterectomy Trial

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) examined a cohort of patients who underwent carotid endarterectomy for symptomatic high grade and moderate-high grade stenosis in order to assess the benefit of this type of intervention. The study was conducted over a 10 year period and comprised 1415 patients in order to assess the effectiveness and durability of carotid endarterectomy (Ferguson et al, 1999).

The NASCET study examined the outcomes of carotid endarterectomy in moderate-high grade stenosis (50-69%) and in high grade stenosis (>70%) and found that the benefit of carotid endarterectomy was limited to those with a symptomatic 70% to 99% ICA stenosis (Moneta et al, 1993). Barnett et al (1998) found that patients with a 50-69% stenosis were found to have only a moderate reduction in stroke risk while patients with <50% stenosis showed no benefit to surgery.
The NASCET study showed an overall rate of perioperative stroke and death of 6.5% with a rate of permanently disabling stroke and death of 2.0%. The results of the NASCET study led to the conclusion that carotid endarterectomy is a durable procedure (Ferguson et al, 1999).

As a result of the benefit of carotid endarterectomy being limited to patients with a symptomatic >70% stenosis, the NASCET study was instrumental in creating demand for a new grading criterion for internal carotid artery duplex. The NASCET study calculated the degree of stenosis angiographically by expressing the narrowest diameter of the ICA as a percentage of the normal vessel diameter distal to the bulb. By comparing the angiogram results to that of carotid duplex ultrasound results it was determined by Moneta et al (1993) that an ICA PSV/CCA PSV ratio of >4.0 provided the greatest sensitivity for the detection of a 70% to 99% stenosis.

2.2.8.2 European Carotid Surgery Trial

The European Carotid Surgery Trial (ECST) comprised of 3018 patients and examined the effect of carotid endarterectomy in this cohort of patients. Initial results showed that surgical intervention is only beneficial in patients with a ≥80% stenosis in comparison to the NASCET study which showed a benefit in patients with a >70% stenosis. Rothwell et al (2003) examined the reasons for this discordance and determined that the methods of determining degree of stenosis angiographically varied between the studies. The NASCET method produced lower values for degree of stenosis than the ECST method, but when the ECST angiograms were remeasured using the NASCET method, the results of both studies were consistent and showed that surgery was highly beneficial in patients with a 70% to 99% stenosis and moderately beneficial in patients with a 50% to 69% stenosis.
2.2.8.3 Current Guidelines for Intervention

In 2011 the Society for Vascular Surgery published revised guidelines for the treatment of internal carotid artery stenosis (Ricotta et al, 2011). The guidelines are summarised as follows:

“Optimal medical therapy is recommended as first line therapy for symptomatic patients with <50% stenosis and asymptomatic <60% stenosis, as there is no proven benefit to surgical or radiological intervention. Asymptomatic patients deemed high risk for carotid endarterectomy should also be considered for optimal medical management.

Carotid endarterectomy is recommended as the first line treatment for the majority of symptomatic patients with a 50% to 99% stenosis and for asymptomatic patients with 60% to 99% stenosis, provided the perioperative risk of stroke and death is below 3% to ensure benefit for the patient. Symptomatic >60% stenosis should be considered for surgical intervention in the form of carotid endarterectomy due to the proven reduction in stroke risk provided the patient has a >3 year life expectancy.

Carotid artery stenting is recommended for symptomatic patients with a 50% to 99% stenosis who are at high risk for carotid endarterectomy due anatomical or medical reasons including tracheal stoma, previous irradiation of the neck, prior cranial nerve injury, prior ipsilateral surgery, and severe chronic obstructive pulmonary disease or congestive heart failure. Carotid artery stenting is not recommended for asymptomatic patients.”

2.2.8.4 Risks Associated with Intervention

Carotid endarterectomy is generally the preferred method of surgical intervention as, despite its invasive nature, it has been found to have a lower 30-day incidence of heart attack, stroke, or death than with internal carotid artery stenting (Sidawy et al, 2009).
2.2.9 Summary

This chapter has outlined why internal carotid artery stenosis is a major factor in cerebrovascular accident, the fourth most common cause of mortality in Ireland since 2010. The management of ICAS through risk factor modification and medical therapy has been outlined, as has the treatment of ICAS both surgically and radiologically. International research has shown that ICAS does progress and that progression is linked to a higher incidence of TIA and CVA, with varying rates of progression reported across several studies. Numerous risk factors are associated with ICAS but there is no consensus as to which risk factor or factors are most important in relation to ICAS progression. Frequent follow up of ICAS is beneficial in determining disease progression and several means of determining the most appropriate follow up have been put forward, with recommendations varying from 6 monthly to 2 yearly follow up. However the Society of Vascular Surgeons currently has no specific follow up guidelines.

In the next chapter the methodology used in conducting this study is outlined and in chapters 4 and 5 respectively the data obtained from the Mater Misericordiae University Hospital will be analysed and how it compares to that found in the current literature will be examined.
Chapter III:

Study Methodology
CHAPTER III: STUDY METHODOLOGY

3.1 Patient Selection

All Colour Duplex scans of the carotid arteries performed in the Vascular Laboratory in the Mater Misericordiae University Hospital (MMUH) from January 2007 to December 2009 were retrospectively reviewed by the same experienced vascular physiologist. The inclusion and exclusion criteria outlined below in sections 3.1.1 and 3.1.2 were applied to determine the study group. Patients were followed up until December 2011.

3.1.1 Inclusion Criteria

i. Unilateral or bilateral asymptomatic 50-69% internal carotid artery stenosis. Patients were considered to be asymptomatic if they were asymptomatic at the time of the scan or if their symptoms were not related to carotid artery disease.

3.1.2 Exclusion Criteria

i. Non-haemodynamically significant internal carotid artery stenosis of <50% bilaterally

ii. Internal carotid artery stenosis of >70% bilaterally

iii. History of carotid intervention

3.2 Internal Carotid Artery Stenosis Surveillance

Patients who met the inclusion criteria were then entered into the surveillance program as outlined below in figure 3.1. The surveillance program consisted of an initial carotid
Review of Patients with Asymptomatic 50-69% Internal Carotid Artery Stenosis over a 3 Year Period

All carotid duplex scans were carried out on one of two machines, a Siemens Acuson S2000 ultrasound system or a Phillips IU22 ultrasound system, using a linear array transducer operating at the optimum frequency (4-9 MHz). Carotid Duplex Scans were performed following the standard protocol described by the Society of Vascular Technologists of Great Britain and Ireland (Cole et al, 2001) and as outlined in Appendix 1.

All scans performed were assessed using the NASCET grading criteria shown in Appendix 2.
3.4 Data Collection

All data was collected retrospectively. Scan reports are stored electronically in the MMUH and the results of 4573 patients were initially analysed to determine the degree of stenosis at their first visit. Following this initial assessment, the study group of patients with a 50-69% unilateral or bilateral stenosis was determined, and their follow up scans were also analysed and the degree of stenosis was recorded in an excel spreadsheet.

Carotid duplex ultrasound scans images, similar to those shown below in section 3.5, obtained post 2009 are recorded electronically and information which was not reported was determined from these stored images, either from a measurement taken during the scan or, where a suitable image was available, using post processing techniques. Scans images from pre 2009 were printed out during the scan and these hard copies were scanned and stored digitally. These digital images were analysed for additional information however post processing was not possible due to the nature of the images.

Risk factors were assessed for the study group only. This was done by first by checking scanned referral letters from GPs and correspondence from hospital consultants to GPs. Where detailed medical histories were provided in these letters, no further checks were deemed necessary. In the absence of a sufficient medical history, hospital charts were obtained and assessed to determine which risk factors were present. A number of patient charts are stored off site and due to the financial implications involved in accessing them and the unfunded nature of this study, it was not possible to access them for the purpose of this study.
3.5 Statistical Methods Used

Data for the study group was analysed using Microsoft Excel 2010. Means and standard deviations were calculated using the standard formulas while univariate analysis was performed on the risk factors obtained. The progression and non-progression groups were analysed using the standard t-test to obtain p-values.

The “p-value” is a statistical determination as to whether two sets of data are the same, or as to whether they are different. So for example if a risk factor such as the patients smoking history is considered, when the two groups of patients are compared; those with stenosis progression and those with no progression; a p-value < 0.05 indicates that there is a statistical difference between the two groups of patients, while a p-value > 0.05 indicates no difference between the two groups for the variable under consideration. A p-value close to 1 would suggest the data is almost identical.

The statistical analysis on the risk factors was undertaken on a univariate basis, where each risk factor was considered separately.

It would have been interesting to undertake a multi-variate analysis where all risk factors were considered simultaneously, however the sub-group of patients for which all such data was available was skewed and not representative of the overall patient cohort (see section 4.4)

3.6 Summary

All patients who attended the vascular lab between January 2007 and December 2009 were retrospectively reviewed and those presenting with a 50-69% internal carotid artery stenosis were followed up for three to five years until December 2011. The results of their carotid duplex scans and the risk factors recorded are analysed in the following chapter, chapter 4.
Chapter IV

Results
CHAPTER IV: RESULTS

The results of Carotid Duplex studies for all patients referred to the Vascular Laboratory between the 1st of January 2007 and the 31st of December 2009 were assessed to determine the suitability of the patients for inclusion in this study.

4.1 Determining the Study Group

**Figure 4.1: Internal carotid artery stenosis at initial scan for all patients scanned from January 2007 to December 2009**

As you can see in figure 4.1, 1098 carotid arteries were found to have a carotid artery stenosis of 50-69% on colour duplex ultrasound at their initial scan. 7151 carotid arteries presented with a <50% stenosis, 790 carotid arteries presented with a >70% stenosis, 94 carotid arteries were post-operative and 13 carotid arteries were not imaged.
The above flow chart details how the final study group was determined. From the initial 4573 patients reviewed, 876 patients had a 50-69% stenosis unilaterally or bilaterally. The remaining 3697 patients had a stenosis of <50% or >70% bilaterally and were therefore eliminated from the study.

Of the 876 patients with a unilateral or bilateral 50-69% stenosis in their initial scan, a further 287 patients were eliminated from the study. Of these, 241 patients were excluded from the study as follow up was not completed for a number of reasons including repeated non-attendance for scans, not a suitable candidate for surgery, and death prior to follow up. The remaining 46 patients were excluded as they had previously undergone carotid artery intervention.

This left a total of 589 patients to be included in the study group for analysis.
4.2 Analysis of Study Group

A total of 589 patients were included in the study group for analysis.

**Figure 4.3: Patient demographics - Study group by age and gender**

The mean age of the study group was 71.3 ± 9.0 years. Of this group, 353 patients were male (59.9%) with a mean age of 70.6 ± 8.3 years, and 236 were female (40.1%) with a mean age of 72.3 ± 9.9 years (fig. 4.3).
Figure 4.4: Percentage of patients who did not progress from a 50-69% stenosis to a >70% stenosis versus the percentage patients who did progress from a 50-69% stenosis to a >70% stenosis

Of the 589 patients included in the study, 102 patients (17.3%) were found to have progressed to a >70% stenosis over the time frame of the study and the remaining 487 patients (82.7%) did not progress to a >70% stenosis over the study timeframe (fig 4.4).
Figure 4.5: Analysis of study group by gender and by whether their stenosis progressed to a >70% stenosis

Of the 236 females, 32 (14%) were found to have progressed, while 70 of the 353 males (20%) were found to have progressed (fig. 4.5).

Figure 4.5 shows that a higher percentage of males progressed to a >70% stenosis over the study timeframe.
**Figure 4.6: Patients who progressed to a >70% stenosis broken down by age and gender**

Of the 102 patients that were found to have progressed to a >70% internal carotid artery stenosis, the mean age at progression was 71.5 ± 7.4 years. The mean age of the 32 females was 71.9 ± 6.2 years and the mean age of the 70 males was 71.2 ± 8.0 years (fig. 4.6).

As evidenced by the red bars, more males patients progressed to a >70% stenosis than female patients across every age category except between the ages of 70 and 74 when 11 females progressed versus 10 males. This is likely due to the higher number of male patients in the study.
**Figure 4.7: Time taken for 50-69% stenosis to progress to >70% stenosis**

![Graph showing the time taken for 50-69% stenosis to progress to >70% stenosis](image)

Figure 4.7 shows the time taken for a 50-69% stenosis to progress to a >70% stenosis. The red line shows the accumulative number of patients who had progressed by each time point. The blue dots shows the number of patients who had progressed by the end of each year.

The blue dots show that, of the 102 patients who progressed to a >70% ICA stenosis, 23 patients (22.5%) progressed within 1 year of their initial scan. A total of 65 patients (64%) progressed by 2 years, 84 patients (82%) progressed by 3 years, 100 patients (96%) progressed by 4 years and 100% of patients who progressed had done so by 5 years post initial scan. A total of 51 patients (50%) progressed did so by 1.4 years. As evidenced by figure 4.7, increments of 1.4 years approximate an exponential relationship.
The average time to the first follow up was 1.11±0.49 years. The average time to the second follow up was 1.07±0.37 years. The average time to the third follow up was 1.02±0.29 years. The average time to fourth follow up was 0.96±0.25 years. Despite annual follow up appointments being scheduled for 1 year ± 1 month after the current scan, figure 4.8 shows that there is significant variance in the time which elapsed between follow up hospital visits attended by the patients in the study group.
As each patient has two carotid arteries which can potentially progress to a high grade stenosis requiring surgery it was necessary to evaluate both the number of patients who progressed to surgical intervention and the number of carotid arteries requiring intervention.

Of the 102 patients who progressed to a >70% ICA stenosis, 45 patients (44.1%) had surgical intervention. The remaining 57 patients (55.9%) did not have surgical intervention during the study time frame.

A total of 108 carotid arteries demonstrated progression of ICA stenosis to >70%. Of these, 48 carotid arteries (44.4%) had surgical intervention; the remaining 60 carotid arteries (55.6%) did not.

Surgical intervention is not recommended for asymptomatic patients >80 years of age. A total of 21 of the patients (20.6%) who progressed to a >70% ICAS were >80 years of age. Of these 21 patients, 76.2% had no surgical intervention and 23.8% underwent surgical intervention.
4.3 Risk Factor Analysis for Entire Study Group

Risk factor data was not included for all patients for a number of reasons including unavailability of charts and data not recorded in charts. The number of patients with data available for each risk factor is outlined in table 4.2. Risk factors prevalence in the progression and non-progression groups were compared and were assessed using the standard t-test with the resultant p-values outlined below in table 4.2. A p-value of <0.05 indicates that the risk factor in question is a statistically significant risk factor for internal carotid artery progression. A p-value of >0.05 indicates that the risk factor in question has no statistically significant relationship with internal carotid artery progression.

4.3.1 Risk Factors

The risk factors analysed in this study were chosen based on a review of the current literature and the patient information available. The literature highlights a number of risk factors that may contribute to the progression of ICAS. These are outlined in Section 2.2.5.

4.3.1.1 Determining the Risk Factors

The presence or absence of risk factors was determined by the definitions outlined in Table 4.1.

Table 4.1: Definitions of Risk Factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Definition of Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Gender was assigned based on the gender recorded in the patients’ medical chart.</td>
</tr>
<tr>
<td>Cardiac History</td>
<td>Cardiac history was determined by reviewing patient charts. A positive cardiac history included CABG, AVR, MVR, PTCA, MI, Angina, A Fib, A Flutter, ICD, Pacemaker, SVT, VT, PFO</td>
</tr>
<tr>
<td>Risk factor</td>
<td>Definition of Risk Factor</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Previous CVA/TIA</td>
<td>Previous CVA/TIA was determined by reviewing patient charts.</td>
</tr>
<tr>
<td>Smoking</td>
<td>Smoking history was self-reported by the patient and recorded by either their GP or a doctor in the hospital.</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Patients were considered to be diabetic if they were formally diagnosed with diabetes or if they were prescribed medications to treat diabetes. No information was available on patient adherence to medications, effectiveness of medications, control of diabetes.</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Patients were considered to be hypertensive if they were formally diagnosed with hypertension or if they were prescribed medications to treat hypertension. No information was available on patient adherence to medications, effectiveness of medications, control of hypertension.</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Patients were considered to be hypertensive if they were formally diagnosed with hypertension or if they were prescribed medications to treat hypertension. No information was available on patient adherence to medications, effectiveness of medications, control of hypercholesterolemia.</td>
</tr>
<tr>
<td>Statin Use</td>
<td>Patients were considered to be using statins if they had been prescribed by a doctor. No information was available on patient adherence to medications, effectiveness of medications.</td>
</tr>
<tr>
<td>Antiplatelet Use</td>
<td>Patients were considered to be using antiplatelet medications if they had been prescribed by a doctor. No information was available on patient adherence to medications, effectiveness of medications.</td>
</tr>
<tr>
<td>IMT</td>
<td>Intima-Media Thickness is measured on a B-mode image of the common carotid artery. A measurement is taken 2cm proximal to the carotid bifurcation and measures the distance between the intima and media. Where IMT measurement was not taken during the scan and post-processing techniques were available, IMT measurement was performed retrospectively provided an appropriate image was available.</td>
</tr>
</tbody>
</table>
Table 4.2: Risk factor analysis for entire study group detailing number of patients for whom the risk factor information was recorded and the resultant p-values

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No. patients with risk factor recorded</th>
<th>p-value (p = &lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet Use</td>
<td>371 (63%)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Cardiac History</strong></td>
<td><strong>306 (52%)</strong></td>
<td><strong>0.04</strong>*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>264 (45%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Gender</td>
<td>589 (100%)</td>
<td><strong>0.02</strong>*</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>329 (56%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Hypertension</td>
<td>337 (57%)</td>
<td>0.15</td>
</tr>
<tr>
<td>IMT</td>
<td>245 (42%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Previous CVA</td>
<td>298 (51%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Smoking</td>
<td>280 (48%)</td>
<td><strong>0.01</strong>*</td>
</tr>
<tr>
<td>Statin Use</td>
<td>371 (63%)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Table 4.2 outlines the risk factors analysed in the left hand column. The middle column shows the number of patients for whom the risk factor information was recorded and the right hand column shows the p-value recorded. A significant correlation between a risk factor and disease progression was taken to be a p-value of <0.05 and risk factors with a significant correlation to disease progression are highlighted in red and italicised.

When comparing those who progressed to develop a significant ICA stenosis to those who did not progress to develop a significant stenosis, a significant correlation to ICAS progression was identified for 3 risk factors. A significant history of cardiac disease found to be a significant risk factor for ICAS progression (p = 0.04). Current and ex-smokers were also found to be at increased risk of ICAS progression compared to non-smokers (p = 0.01), and males were found to be at higher risk of progression than females (p = 0.02). The significant risk factors are outlined below. All other risk factors can be viewed in Appendix 5.
Figure 4.10: Positive cardiac history in the no progression group compared to the progression group across the entire study group

Cardiac history was available for 306 of the 589 patients included in the study. In the No Progression group, 82% of patients were recorded as having a significant cardiac history. In the Progression group 92% of patients were recorded as having a significant cardiac history (fig 4.10). Cardiac history is a significant predictor of progression of ICAS ($p = 0.04$).
Gender data was available for 589 of the 589 patients included in the study. In the No Progression group, 58% of patients were male and 42% were female. In the Progression group 69% of patients were male and 31% were female (fig 4.1). Male gender is a significant predictor of progression of ICAS ($p = 0.02$).
Smoking data was available for 280 of the 589 patients included in the study. In the No Progression group, 31% of patients were recorded as being current smokers and 20% were recorded as being ex-smokers, giving 52% with a positive smoking history. In the Progression group 34% of patients were recorded as being current smokers and 34% were recorded as being ex-smokers, giving 68% with a positive smoking history (fig 4.12). Smoking history is a significant predictor of ICAS progression with smokers and ex-smokers being significantly more likely to progress to a >70% ICAS ($p = 0.01$).
Figure 4.13: Age at progression of patients with diabetes, positive smoking history and positive cardiac history

The average age at progression of patients with diabetes was 73±0.65 years. The average age at progression of patients with a positive smoking history was 71.4±6.23 years. The average age at progression of patients with a positive cardiac history was 74.6±6.01 years.

Patients with a positive smoking history begin to progress at an earlier age than those with diabetes, and patients with a positive cardiac history tend to progress at an older age than those with diabetes or a positive smoking history.
4.4 Risk Factors Analysis for Patients with All Data Available

Full risk factor data was available for 153 (26%) of the 589 patients included in the study.

Table 4.3: Risk factor analysis for patients for whom all risk factor data was available and the resultant p-values

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet Use</td>
<td>0.06</td>
</tr>
<tr>
<td>Cardiac History</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.49</td>
</tr>
<tr>
<td>Gender</td>
<td>0.10</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0.25</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.36</td>
</tr>
<tr>
<td>Previous CVA</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td><strong>0.04</strong>*</td>
</tr>
<tr>
<td><strong>Statin Use</strong></td>
<td><strong>0.05</strong>*</td>
</tr>
</tbody>
</table>

Table 4.3 outlines the risk factors analysed in the left hand column and the right hand column shows the p-value recorded. A significant correlation between a risk factor and disease progression was taken to be a p-value of <0.05, and risk factors with a significant correlation to disease progression are highlighted in red and italicised.

A significant correlation to ICAS progression was identified for 2 risk factors. Current and ex-smokers were also found to be at increased risk of ICAS progression compared to non-smokers (p = 0.04), and statin use was also found to be more prevalent in patients who progressed than in those that did not progress (p = 0.05).

As a result of the small number of patients with all data available, the accuracy of the results is questionable and should not be taken as proof of a significant or insignificant
relationship between risk factors and ICAS progression. This is particularly evident when examining the gender spread of this subset as it is not representative of the larger study group. Further information on this analysis can be found in Appendix 6.

A multivariate regression analysis of the risk factors found no significant predictor of ICAS progression.

4.5 Summary

The results of the research presented here show a high rate of internal carotid artery stenosis progression in this cohort of patients with 17.3% of the 589 patients progressing from a 50-69% stenosis to a >70% stenosis over the 5 years of the study. Progression was noted in 14% of female patients and 20% of male patients. Of the patients who progressed, 50% did so within 1.4 years of their initial scan, however a large degree of variation was noted in the time between follow up scans with the average time to first “annual” follow up being 1.11±0.49 years. Of the patients who progressed to a >70% ICAS, 44.1% had surgery within the study timeframe.

On analysis of the entire study group, 3 risk factors were identified with a significant correlation ($p<0.05$) to ICAS progression. A significant history of cardiac disease was found to be a risk factor for ICAS progression ($p = 0.04$). Current and ex-smokers were also found to be at increased risk of ICAS progression when compared to non-smokers ($p = 0.01$), and males patients were found to be at higher risk of progression than female patients ($p = 0.02$).

In the next chapter our results will be compared to the available literature and an attempt will be made to answer the research questions posed in Chapter 1.
Chapter V:

Discussion
CHAPTER V: DISCUSSION

In chapter I a number of research question were posed. In this chapter those questions will be answered and the findings will be compared to the current literature.

5.1 Does asymptomatic carotid artery disease causing a 50-69% internal carotid artery stenosis typically progress to a >70% stenosis?

The NASCET and ESCET studies led to the recommendations that surgical intervention be reserved for asymptomatic patients with a >70% ICAS (Rothwell et al, 2003). The results of the research presented here show a high rate of internal carotid artery stenosis progression in this cohort of patients with 17.3% of the 589 patients progressing from a 50-69% stenosis to a >70% stenosis over the 5 years of the study. This compares favourably to the rates of progression reported in the current literature discussed below. Laipis et al (2000) examined 442 carotid arteries in 332 patients over a 7 year period and found that progression of ICA stenosis occurred in 19% of patients included in their study over that time frame. This is a similar rate of progression to that shown by our research which reports a 17.3% rate of progression in 589 patients over a 5 year period.

A study by Hicks et al (2015) conducted over 7.5 years found that 25.2% of their 258 patients progressed from 50-69% ICA stenosis to severe stenosis of >70%. The work presented here found a lower progression rate of 17.3% despite having a larger cohort of patients with 589 participants. The mean age of the participants was 71.3±9 years in this study and 70±0.55 years (Hicks et al, 2015). The discrepancy in progression rates could be due to the duration of the studies in question as our study followed patients for 5 years as opposed to the 7.5 years examined by Hicks et al (2015).

Jahromi et al (2009) studied 547 patients over 4 years and concluded that the average rate of progression over a 2 year period was not significant. Conversely our research
found that 10.9% of patients had progressed to a >70% ICA stenosis after 2 years of follow up. The age of the participants was similar in both studies with the mean age of the participants in this study being 71.3±9 years versus 72.8±9.5 years (Jahromi et al, 2009). As this study was limited to patients with an initial ICA stenosis of 50-69% where Johromi et al (2009) studied patients with baseline stenosis ranging from 0% to 99%, making a direct comparison between the studies is difficult.

Mansour et al (1999) showed disease progression from 50-79% to >80% in 15.5% of their 344 patients over a 4 year period. While a direct comparison cannot be made to the results of our research due to the differing grading criterion applied in the two studies, there is a marked similarity in the rates of progression noted with our study reporting a rate of progression of 17.3%. The time frames of the studies are also quite similar at 4 years versus 5 years in our study.

Nehler et al (1996) examined the rate of progression of <60% asymptomatic ICA stenosis to asymptomatic >60% ICA stenosis. The cut-off point of 60% is based on the Asymptomatic Carotid Atherosclerosis Study (ACAS) which demonstrated a benefit to prophylactic carotid endarterectomy for patients with a >60% asymptomatic ICA stenosis. They studied 263 patients over a period of 4 years and reported progression in 6.5% of patients after 1.5 years. In a similar study by Lovelace et al (2001) which followed 640 carotid arteries with <60% ICA stenosis for an average of 1.8 years, it was reported that progression to >60% stenosis occurred in 8% of ICAs within that time frame. These are very similar rates of progression to that reported in our research with our study finding 8.4% of patients progressed to a >70% stenosis within 1.4 years of their initial scan.

Mulak et al (1999) found that 9.3% of the at-risk population showed progression of ICA stenosis annually. Garvey et al (2000) followed 905 asymptomatic patients over 10
years and also reported that 9.3% of the at-risk population demonstrated progression of ICA stenosis annually. However both studies included patients with baseline stenosis ranging from <15% to 99% and progression was deemed to have occurred if the percentage stenosis changed to a higher category (mild, moderate, severe, pre-occlusive). Due to the broader range of baseline stenosis included in their study, a direct comparison cannot be drawn to the rate of progression reported in our study which was focused on patients with a baseline stenosis of 50-69%. Also the mean age of the participants was 71.3±9 years in this study versus 65.5 years in both of the above mentioned studies (Mulak et al, 1999 and Garvey et al, 2000) which may also account for the variation in reported rates of ICAS progression.

The progression rate of 17.3% reported in our research is similar to those reported in a number of other studies including the 19% progression rate reported by Laipis et al (2000) and the 15.5% reported by Mansour et al (1999). The progression rates of 6.5% after 1.5 years reported by Nehler et al (1996) and 8% after 1.8 years reported by Lovelace et al (2001) are also comparable to the progression rate of 8.4% after 1.4 years reported in this study. Like these studies, the results of the research presented here show that internal carotid artery stenosis has a significant rate of progression to a >70% stenosis suitable for surgical intervention.

5.2 Is it possible to identify the proportion of patients who go on to develop symptomatic or asymptomatic >70% internal carotid artery stenosis or require surgical intervention?

The results of the research presented here shows a high rate of internal carotid artery stenosis progression in this cohort of patients with 17.3% of the 589 patients
progressing from a 50-69% stenosis to a >70% stenosis over the 5 years of the study. This is consistent with the results reported in a number of other studies, as discussed above in section 5.1. These findings confirm that, with the data currently available to us, it is possible to identify the proportion of patients attending the vascular lab in the MMUH who go on to develop symptomatic or asymptomatic >70% internal carotid artery stenosis or require surgical intervention.

5.3 Is there a benefit to annual Colour Duplex follow-up in patients presenting with an asymptomatic 50-69% internal carotid artery stenosis?

International studies have produced recommendations that follow up of 50-69% ICAS be performed at intervals ranging from 6 months to 2 years, however there are no specific follow up interval guidelines currently outlined by the Society for Vascular Surgery (Ricotta et al, 2011).

Research by Strandness (2001) showed that patients with a <50% stenosis should be followed up annually while patients with a 50-79% stenosis should be followed up 6-monthly. Jahromi et al (2009) suggest that the average rate of stenosis progression over 2 years is not significant and therefore follow up colour duplex scans should be performed at 1-2 year intervals.

Nehler at el (1996) showed that an internal carotid artery PSV of ≥175cm/sec indicated a higher risk of early progression and recommended early vascular laboratory follow up, however did not suggest a follow up interval. Similarly a study by Lovelace et al (2001) showed that patients with < 60% ICA stenosis and a PSV of ≥175cm/sec are more likely to progress to a higher grade stenosis and thus warrant 6-monthly follow up scans, while patients with < 60% ICA stenosis and a PSV of <175cm/sec may benefit from follow up scans every 2 years.
The results of this study showed that of the 102 patients who progressed to a >70% ICA stenosis, 23 patients (22.5%) progressed within 1 year of their initial scan, while a total of 51 patients (50%) progressed by 1.4 years. However, given the large degree of variance in the time between follow up scans reported in this study it is not prudent to suggest that a specific follow up interval be recommended. It would be more beneficial to take a cautious approach and continue with annual follow up scans for this cohort of patients until such time as a more accurate estimate of time to progression can be determined. In order to achieve this, improvements need to be made to the timing of patient attendances and this will be discussed further in section 5.4.

5.4 Is the current follow up programme in the MMUH programme effective in the detection of internal carotid artery stenosis progression?

The current follow up programme in the MMUH calls for annual follow up of patients with a 50-69% internal carotid artery stenosis. When this programme is adhered to, that is to say when patients attend for annual follow up within two weeks of the anniversary of their previous scan, the current follow up programme is effective. However the results of this study have shown that there is a large degree of variation in the time between annual follow ups, with an average time of 1.1±0.49 years noted between the patients’ initial scan and their first follow up. This variation in attendance results in delays in identifying ICAS progression and delays referring asymptomatic patients for surgical consideration. As asymptomatic patients with high grade stenoses are treated surgically in the MMUH, these delays reduce the overall effectiveness of the follow up programme.

When correctly followed by patients the current follow up programme is effective, however improvements need to be made to the timing of patient attendances. The
department has already increased the number of reminder letters sent to patients in the 6 weeks prior to their appointment, and text messages are also being utilised as another means of reminding patients of appointments.

Further improvements could be made by improving patient education regarding the role of carotid duplex ultrasound in the prevention of TIA and CVA in patients with a 50-69% internal carotid artery stenosis. Since 2007, CVA has been the third most common cause of death in Ireland, behind all cancers and ischaemic heart disease and, since 2010, is responsible for two and a half time more deaths annually than breast cancer (Central Statistics Office, 2017). Each year, approximately 10,000 Irish people have a CVA or TIA and approximately 2,000 of these people die as a result of this (Irish Heart Foundation, 2018). Approximately 80% of CVA are ischaemic in nature and occur as a result of significant stenosis of the vessels of the intracranial or extracranial circulation (www.stroke.org.uk, 2015). Internal carotid artery stenosis affects approximately 7% of women and more than 12% of men over 70 years of age (Marquardt et al, 2010).

In spite of these startling statistics, unlike breast cancer, there is no concerted campaign aimed at screening for carotid artery disease. The current Irish Heart Foundation stroke campaign aimed at the general public is focused on the FAST principles and aims to educate people on the symptoms of stroke and the importance of early intervention in preventing permanent disability or death (Irish Heart Foundation, 2018). Similarly the campaign aimed at the medical field focuses on the importance of early intervention in the successful treatment of and recovery from CVA (Irish Heart Foundation, 2018). Neither of these campaigns makes any connection to the role carotid disease in CVA and the benefit of frequent follow up of patients with ICAS in the prevention of CVA. This is an area that could be improved, primarily through patient education.
Patient education could be implemented in two ways; through conversation with either doctors or physiologists, and by providing pamphlets outlining the role of carotid duplex ultrasound in the prevention of TIA and CVA in patients with a 50-69% internal carotid artery stenosis. Improving patient awareness of the increased risk of CVA associated with ICAS progression should lead to improved attendance at follow up appointments.

5.5 Is it possible to identify any predisposing risk factors associated with progression of ICAS?

A number of risk factors for internal carotid artery stenosis progression have been identified across a range of studies; however no consensus has been reached as to which risk factors are the most relevant.

This study identified 3 risk factors with a significant correlation \( p < 0.05 \) to ICAS progression. A significant history of cardiac disease was found to be a risk factor for ICAS progression \( (p = 0.04) \). Current and ex-smokers were also found to be at increased risk of ICAS progression when compared to non-smokers \( (p = 0.01) \), and males patients were found to be at higher risk of progression than female patients \( (p = 0.02) \).

Cardiac history has been shown to correlate to disease progression with ICA stenosis progression correlated to coronary artery disease in a study by Laipis et al (2000). Mansour et al (1999) also reported ischaemic heart disease as a risk factor for disease progression. Hicks et al (2015) found current smokers to be at a higher risk of progression.

Garvey et al (2000) also found 6 risk factors that had a statistically significant effect on time to progression; age, gender, systolic blood pressure, pulse pressure, total cholesterol and HDL-C, while multivariate analysis found that an increase in pulse
pressure and a decrease in HDL-C were the only independent predictors of ICAS progression.

Bots et al (1997) found during the Rotterdam Study that stroke risk increased gradually with increasing IMT, independently of other risk factors. Robertson et al (2012) reviewed several studies to assess the role of IMT as a predictor of CVA and found that in one study (Rotterdam Study) an IMT of >0.84mm was predictive of stroke while another study (Malmo Diet and Cancer Study) found that the IMT was associated with the incidence of CVA. Gardin et al (2014) who also found that carotid IMT improves 10-year risk prediction of CVD and stroke.

Several studies also examined age, gender, diabetes, hypertension, hypercholesterolemia, smoking, antiplatelet use and cardiac history and found no significant correlation to ICAS progression (Nehler et al, 1996; Laipis et al, 2000; Moneta et al, 1989).

The results of this study appear to compare favourably to the results reported in the literature, however the risk factor data available for analysis was incomplete. As the data for this study was retrospectively it was frequently found that the risk factors being examined were not recorded. Gender is the only risk factor recorded for all patients. All other risk factors are reported for between 42% and 63% of patients. As a result of this, the only risk factor which can be certain to have produced a valid result is gender, and male gender was found to be a significant risk factor for ICAS progression ($p=0.02$).

It is not possible to accurately identify any other predisposing risk factors associated with progression of ICAS due to incomplete data. In order to remedy this, it is recommended that for future studies the vascular physiologist performing the scan records the relevant data in a comprehensive manner using a data collection record such as that shown in Appendix 3.
The benefit of this tool is that it would hold all the pertinent information in one location. The patients’ demographics such as age and gender, as well as vital statistics such as height, weight, body mass index and blood pressure can all be recorded in one place. This data collection sheet also allows for a comprehensive medical history to be taken with space available to record the relevant details from the patients’ medical history such as incidents of CVA or TIA, the symptoms experienced and when it occurred.

Risk factors are recorded with a number of the most relevant risk factors selected for inclusion. These risk factors include the smoking history of the patient and of the individuals with whom the patient resides, as well as hypertension, hypercholesterolemia and diabetes, as well as recording the medications used to treat these conditions and any other relevant medications being taken such as antiplatelet medications.

Cardiac history, particularly atherosclerotic cardiac disease, can also have a close link to progression of carotid artery disease and a detailed cardiac history can be recorded on this data collection sheet, as well as the medications used in the treatment of these conditions.

Due to the incomplete risk factor data recorded for the patients included in this study, it is only possible to accurately identify male gender as a risk factor for ICAS progression ($p=0.02$). The use of a data collection sheet, such as the one shown in appendix 3, by the vascular physiologists performing the scans would allow for a comprehensive patient history to be obtained and would benefit future studies.
5.6 Study Limitations

Over the course of this study, a number of limitations were identified, primarily due to the retrospective nature of the study and also due to the variance in the timing of patient attendance for follow up.

The retrospective nature of this study was a limiting factor in terms of the availability of data. As the data required for this study was not known when the scans were being performed, and this data was being recorded by non-consultant hospital doctors (NCHDs) incomplete data was frequently recorded for patients; with risk factors such as smoking history, diabetes, hypertension and hypercholesterolemia not always documented. It is recommended that for future studies data be captured in a comprehensive way by the vascular physiologist performing the scan in order to tightly control data collection and ensure that all pertinent risk factor information is gathered during all visits. A sample data collection sheet is shown in Appendix 3 and is discussed above in section 5.6.

The frequency of patient attendance for follow up was also an issue for this study. The timing of attendance for appointments was inconsistent with a great deal of variance noted. This could be remedied by improving patient education and emphasising the role of carotid duplex ultrasound in the prevention of TIA and CVA in patients with internal carotid artery stenosis progression. Improving patient awareness of the increased risk of CVA associated with ICAS progression may lead to improved attendance at follow up appointments.
Another disadvantage of the retrospective nature of the study is the inability to adequately assess patients’ adherence to medical therapy. Records of medications prescribed are recorded in many cases but there is no indication as to whether patients were adhering to their prescriptions or if their medications were effective. The addition of blood tests to assess cholesterol levels and coagulability levels would be beneficial as it would allow for the assessment of whether optimal medical therapy of risk factors has been achieved and would therefore allow the impact of optimal medical therapy on the rate of ICAS progression to be assessed.

In the early stages of the study, routine IMT measurement was not a part of the MMUH carotid scanning protocol and therefore was not recorded. Scan images were saved to a secure server within the hospital where they are available to view, however due to the nature of the scanned images, post processing techniques proved inconsistent making it impossible to retrospectively obtain accurate IMT measurements. IMT measurement was introduced as a part of the carotid scanning protocol in 2010 and is consistently recorded by the vascular physiologists which will be beneficial for future studies. The current method of digital image storage will also be of benefit when assessing plaque type and morphology as the images are of a high quality making retrospective analysis an achievable aim.
Chapter VI:

Conclusion and Recommendations
CHAPTER VI: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion and Recommendations

The purpose of this study was primarily to assess if asymptomatic carotid artery disease causing a 50-69% internal carotid artery stenosis typically progresses to a >70% stenosis which may require intervention. As 17.3% of patients did in fact progress over the 5 years of the study it can be concluded that there is a significant rate of ICAS progression noted in this cohort of patients. 44.1% of patients had surgery during the study timeframe, while 55.9% did not. 16 of these patients (15.7%) were not candidates for surgery due to their advanced age (>80 years).

These results have led to recommendations for alterations to the current follow up protocol. Asymptomatic patients over 80 years of age are not currently recommended for surgical intervention (Naylor et al, 2017). As such there is no clear benefit to following up this cohort of patients and it is recommended that they be discharged to their referring doctor. A summary of the recommended changes to the follow up protocol are outlined in figure 6.1.

Figure 6.1: Recommended Follow Up Protocol
This study also aimed to evaluate the necessity and effectiveness of annual Colour Duplex ultrasound follow-up in patients presenting with 50-69% internal carotid artery stenosis. Due to the large degree of variance in the timing of the ‘annual’ follow ups, it is difficult to make a recommendation on the time to be allowed between consecutive follow ups, however annual follow up would appear to benefit the majority of patients and allow for timely intervention in cases of disease progression.

As a result of variance in timing of annual follow up, it is recommended that policy changes be implemented in the hospital to ensure better patient compliance with annual follow up. The MMUH has already implemented a more rigorous approach to reminding patients of their impending appointments. Better patient education with regard to the risks associated with TIA and CVA, and the importance of carotid duplex surveillance in preventing potential disability or death may also improve patient attendance for follow up scans. This could be implemented in various forms including through conversation with physicians or vascular physiologists, information leaflets and it could potentially be linked with the current FAST campaign run by the Irish Heart Foundation, as discussed above in section 5.4.

The retrospective nature of this study was a limiting factor in the availability of data. It is recommended that for future studies data be captured in a comprehensive way by the vascular physiologist performing the scan in order to tightly control data collection and ensure that all pertinent risk factor information is gathered during all visits, as discussed above in section 5.6. A sample data collection sheet is shown in Appendix 3.
6.2 Further Research

An area that was not examined by our study is the effect of initial PSV and EDV on the rate of ICAS progression. As these measurements are routinely recorded during a carotid scan, this is an area that may benefit from further investigations.

The relationship between atherosclerotic cardiovascular disease (CVD) and ICAS progression may also be better understood if specific cardiac history was recorded. The accurate and consistent recording and reporting of IMT may also be important in determining the relationship between atherosclerotic CVD and ICAS.

Due to the retrospective nature of the study it was not possible to adequately assess patients’ adherence to medical therapy. The addition of blood tests to assess cholesterol levels and coagulability levels would also be beneficial as it would allow the impact of optimal medical therapy on the rate of ICAS progression to be assessed.
References
References


Healthcare Professionals From the Stroke Council of the American Heart Foundation” Stroke. 32:280-299.


Review of Patients with Asymptomatic 50-69% Internal Carotid Artery Stenosis over a 3 Year Period


Appendices
Appendix 1: Procedure for Duplex Ultrasound of Carotid Arteries

Duplex ultrasound of the carotid arteries is performed according to the protocol described by the Society for Vascular Technology of Great Britain and Ireland (Cole et al, 2001), and is as follows.

1. Start in transverse at the proximal common carotid artery; identify the side of the neck (right or left) and the vessel, and orient the screen as to medial and lateral.
2. Move distally in the common carotid artery. Identify the bifurcation and branches, and image as far distally as possible in the internal carotid artery.
3. Move back down the internal carotid artery to the proximal common carotid artery.
4. Identify and assess any lesions at all levels.
5. Rotate to longitudinal in the proximal common carotid artery; orient the screen as to cephalad and caudal (head to left, feet to right of image).
6. Move distally in the common carotid artery; identify the bifurcation in the middle of the screen, keep the common carotid artery imaged clearly while angling medially and laterally to identify the internal and external carotid arteries.
7. Measure the IMT in the distal common carotid artery, 2cm back from the bifurcation (fig A1.1).
Figure A1.1: Common Carotid Artery IMT Measurement

8. Image as far distally as possible in the internal carotid artery.
At all levels, use different approaches to optimise the image and to assess lesions.
Then move back down to the proximal common carotid artery.

Figure A1.2: (a) B-mode Transverse (b) Colour Transverse

9. Scan once through in transverse (fig A.12) and longitudinal (fig A1.3) in B-mode to assess the grey-scale image and then once again with colour flow to look for abnormal velocity changes, identify difficult anatomy, delineate irregularities in plaque, etc.
10. Use the colour display to localise high-velocity jets for placement of the spectral Doppler sample volume.

11. In a longitudinal plane, obtain Doppler samples from the common, external and internal carotid arteries.
12. All velocity measurements must be performed at the angle of 60 degrees with the Doppler cursor aligned parallel to the vessel walls (fig A1.4).

13. To ensure complete interrogation, precisely track the spectral Doppler cursor throughout the entire common and internal carotid arteries.

14. At least one representative spectral waveform is recorded proximally and distally in the common carotid artery, and in the proximal, mid and distal internal carotid artery.

15. Doppler information is used to identify the presence, absence, and direction of flow and the severity of stenosis, if present.

16. In the presence of pathology, spectral waveforms should be recorded proximal, within, and distal to the lesion, walk the sample volume through any area of atheroma to record velocity changes and turbulence (fig A1.5).

Figure A1.5: Spectral waveforms (a) proximal to, (b) within and (c) distal to a lesion
17. Measurements include peak systolic velocity (PSV) and end diastolic velocity (EDV) in the ICA and the CCA (fig A1.6).

**Figure A1.6**: PSV and EDV in (a) Common Carotid Artery (b) Internal Carotid Artery

18. A representative spectral waveform, velocity and determination of flow direction are recorded in the proximal external and vertebral arteries.
Appendix 2: Interpretation of Carotid Duplex Scanning

As per NASCET study (Barnett et al, 1998) “ICA stenosis” compares the diameter of the lumen at the most severely stenosed site in the ICA, to the lumen of normal ICA distal to bulb.

- ICA / CCA ratio >3 times <4 times = 60% stenosis
- ICA / CCA ratio >4 = 70% stenosis
- ICA / CCA ratio >4.5 times = >75% stenosis

Internal Carotid Artery Velocity Measurement

Doppler information – at site of stenosis, also proximal and distal

<table>
<thead>
<tr>
<th>Velocity Criteria (cm/sec)</th>
<th>ICA Stenosis</th>
<th>Spectral Broadening</th>
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<tr>
<td>PSV ≤110</td>
<td>0-29%</td>
<td>No</td>
</tr>
<tr>
<td>PSV 110-125</td>
<td>30-49%</td>
<td>Mild</td>
</tr>
<tr>
<td>PSV &gt; 125 and ICA/CCA ratio of &lt;4</td>
<td>50-69%</td>
<td>Complete</td>
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<tr>
<td>PSV &gt; 125 and EDV ≥ 110</td>
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<tr>
<td>PSV &gt; 125 and EDV ≥ 200</td>
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<td>Not relevant</td>
</tr>
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</table>

Trickle flow: Damped low velocities with <1mm patent lumen = 99% Stenosis
No Colour flow or Doppler signal in a well imaged vessel: 100% Total Occlusion
*CCA/ECA stenosis = Doubling of velocities >50% stenosis
Trebling of velocities >75% stenosis
Appendix 3: Risk Factor Record Sheet

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<th>Initials: __________</th>
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<td>Age: _______</td>
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<tr>
<td>BP: <strong>/</strong></td>
<td>Height: ___</td>
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<th>years</th>
<th>no./day</th>
<th>Ex</th>
<th>years</th>
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# Appendix 4: Risk Factor Data

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Appendix 5: Risk factor analysis for entire study group

Figure A5.1: Antiplatelet use in the no progression group compared to the progression group across the entire study group

Data on antiplatelet prescription was available for 371 of the 589 patients included in the study. In the No Progression group, 89% of patients were recorded as being prescribed antiplatelet medication. In the Progression group 94% of patients were recorded as being prescribed antiplatelet medication. Antiplatelet use is not a significant predictor of ICAS progression ($p = 0.11$).
Figure A5.2: Positive history of diabetes in the no progression group compared to the progression group across the entire study group

Diabetes data was available for 264 of the 589 patients included in the study. In the No Progression group, 46% of patients were recorded as having diabetes. In the Progression group 45% of patients were recorded as having diabetes (fig A5.2). Diabetes is not a significant predictor of ICAS progression ($p = 0.47$).
Hypercholesterolemia data was available for 329 of the 589 patients included in the study. In the No Progression group, 91% of patients were recorded as having hypercholesterolemia. In the Progression group 89% of patients were recorded as having hypercholesterolemia (fig A5.3). Hypercholesterolemia is not a significant predictor of ICAS progression ($p = 0.37$).
Hypertension data was available for 337 of the 589 patients included in the study. In the No Progression group, 93% of patients were recorded as having hypertension. In the Progression group 96% of patients were recorded as having hypertension (fig A5.4). Hypertension is not a significant predictor of ICAS progression ($p = 0.15$).
**Figure A5.5:** Intima Media Thickness in the no progression group compared to the progression group across the entire study group

The X-axis shows the thickness of the IMT in centimeters, while the number of patients is shown on the Y-axis. The blue line represents the IMTs recorded for patients who did not progress to a $>$70% stenosis. The red line represents the IMTs recorded for patients who did progress to a $>$70% stenosis.

IMT measurement was recorded at the first visit for 245 of the 589 patients included in the study. IMT at initial scan is not a significant predictor of ICAS progression ($p = 0.48$).
Figure A5.6: Previous history of CVA in the no progression group compared to the progression group across the entire study group

CVA history was available for 298 of the 589 patients included in the study. In the No Progression group, 49% of patients were recorded as having had a CVA. In the Progression group 46% of patients were recorded as having had a CVA (fig A5.6). Previous CVA is not a significant predictor of ICAS progression ($p=0.38$).
Figure A5.7: Statin use in the no progression group compared to the progression group across the entire study group

Data on statin prescription was available for 371 of the 589 patients included in the study. In the No Progression group, 65% of patients were recorded as being prescribed statins. In the Progression group 68% of patients were recorded as being prescribed statins (fig A5.7). Statin use is not a significant predictor of ICAS progression ($p = 0.35$).
Appendix 6: Risk factor analysis of patients for whom all risk factor data was available

Figure A6.1: Antiplatelet use in the no progression group compared to the progression group for patients with all risk factor data available

In the No Progression group, 90% of patients were recorded as being prescribed antiplatelet medication. In the Progression group 100% of patients were recorded as being prescribed antiplatelet medication (fig A6.1). Antiplatelet use is not a significant predictor of ICAS progression ($p = 0.10$).
Figure A6.2: Positive cardiac history in the no progression group compared to the progression group for patients with all risk factor data available

In the No Progression group, 76% of patients were recorded as having a significant cardiac history. In the Progression group 91% of patients were recorded as having a significant cardiac history (fig A6.2). Cardiac history is not a significant predictor of progression of ICAS ($p = 0.06$).
Figure A6.3: Positive history of diabetes in the no progression group compared to the progression group for patients with all risk factor data available

In the No Progression group, 41% of patients were recorded as having diabetes. In the Progression group 41% of patients were recorded as having diabetes (fig A6.3). Diabetes is not a significant predictor of ICAS progression ($p = 0.49$).
In the No Progression group, 60% of patients were male and 40% were female. In the Progression group 45% of patients were male and 55% were female (fig A6.4). Gender is not a significant predictor of progression of ICAS ($p = 0.10$)
In the No Progression group, 85% of patients were recorded as having hypercholesterolemia. In the Progression group 91% of patients were recorded as having hypercholesterolemia (fig A6.5). Hypercholesterolemia is not a significant predictor of ICAS progression ($p = 0.25$).
In the No Progression group, 93% of patients were recorded as having hypertension. In the Progression group 91% of patients were recorded as having hypertension (fig A6.6). Hypertension is not a significant predictor of ICAS progression ($p = 0.15$).
In the No Progression group, 35% of patients were recorded as having had a CVA. In the Progression group 27% of patients were recorded as having had a CVA (fig A6.7). Previous CVA is not a significant predictor of ICAS progression ($p = 0.24$).
In the No Progression group, 21% of patients were recorded as being current smokers and 15% were recorded as being ex-smokers, giving a total of 36% with a positive smoking history. In the Progression group 36% of patients were recorded as being current smokers and 23% were recorded as being ex-smokers giving a total of 59% with a positive smoking history (fig A6.8). Positive smoking history is a significant predictor of ICAS progression with smokers and ex-smokers being significantly more likely to progress to a >70% ICAS ($p = 0.04$).
In the No Progression group, 81% of patients were recorded as being prescribed statins. In the Progression group 95% of patients were recorded as being prescribed statins (fig A6.9). Statin use is a significant predictor of ICAS progression ($p = 0.047$).